

**REMARKS**

This Response, filed in reply to the Office Action dated November 3, 2010, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 19, 20 and 31-37 are rejected in the outstanding Office Action.

No new matter is added by way of this response. Consideration of the remarks herein is respectfully requested.

**Claims 19, 20, 31, 32 and 35-37 are Patentable Under 35 U.S.C. § 102(b)**

1. On page 2 of the Office Action, Claims 19, 20, 32 and 35-37 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Fleming *et al.* (*i.e.*, U.S. Patent No. 6,423,501 or WO 98/25647), essentially for the reasons set forth in the Office Action mailed April 7, 2010.

2. On page 5 of the Office Action, Claims 19, 20, 31, 32 and 35-37 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Curd *et al.* (WO 00/67796), essentially for the reasons set forth in the Office Action mailed April 7, 2010.

The Office continues to sustain these rejections on the proposition that the disclosure of each claim element *individually* (*e.g.*, CD81, inflammatory bowel disease, and an antibody) within *different* laundry lists (each of which describes myriad alternatives for each element) constitutes disclosure of the specific combination claimed by Applicants, and thus is proper.

In maintaining that this picking-and-choosing is not impermissible, the Office argues that the claim elements selected from the laundry list disclosures are sufficiently related to one another to find anticipation. For example, the Office contends that “all the diseases” recited in Fleming *et al.* and Curd *et al.* are “directly related” as being autoimmune diseases, and that “all

the antagonists” of Curd *et al.* are “directly related” as being B-cell markers. That is, the Office attempts to distinguish the present case from *In re Arkley*, where the court held that the picking and choosing of different claim elements is improper where the different claim elements are not “directly related” to one another by the teachings of the cited reference.

Further, in response to Applicants’ arguments that Fleming *et al.* and Curd *et al.* provide no more than generic disclosures, because they merely recite laundry lists of possible targets, diseases and agents from which Applicants’ specific *species* must be selected (*i.e.*, the species being the specific combination of CD81, inflammatory bowel disease, and antibody claimed by Applicants), the Office contends that the relied-upon portions of Fleming *et al.* and Curd *et al.* do not constitute generic disclosures, citing M.P.E.P. § 2131.02, because each element is explicitly named. On this basis, the Office believes that the cited genus-species case law is inapplicable.

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

Applicants respectfully disagree with the Office’s logic as to why (a) the rejection does not constitute impermissible picking and choosing, and (b) why the laundry lists of Fleming *et al.* and Curd *et al.* - when relied upon in conjunction as the Office has done - do not constitute a generic disclosure. For the reasons set forth below, the rejections are sustained on flawed logic, are inconsistent with relevant law, and must therefore be withdrawn.

First, turning to the Office’s reasoning as to why the selection of the different claim elements from Fleming *et al.* and Curd *et al.* does not constitute impermissible picking-and-choosing, the Office attempts to justify the rejection by arguing that the items listed within a given laundry list are directly related to each other. For example, the Office argues that “all the diseases” recited in Fleming *et al.* and Curd *et al.* are “directly related” as being autoimmune

diseases, and that “all the antagonists” of Curd *et al.* are “directly related” as being B-cell markers. This argument, however, is predicated on a misunderstanding of the law. The relevant “direct” relationship in the instant case is not that asserted in the rejection. To the contrary, *Arkley* makes clear that the “direct relationship” must be *between the specific claim elements themselves*. Accordingly, in the instant case, the direct relationship must be between those elements selected from *different* laundry lists (*i.e.*, CD81, inflammatory bowel disease, and an antibody), not merely between the alternatives recited within each laundry list.

Indeed, under the logic set forth in the rejection, it would appear that even in those instances where the courts have found no anticipation of a chemical species by a generic chemical formula, because picking-and-choosing of specific substituents for several different moieties was necessary, *see In re Arkley*, anticipation would have been proper. By way of example, all the possible substituents disclosed for a given position on a chemical formula could be argued to be “directly related” to each other by the teachings of the cited reference because they are all disclosed as being suitable for use at this position.

As noted above, the relevant relationship, as expressly articulated in *Arkley*, is whether there exists a direct relationship linking together all the elements *claimed*. Applicants reiterate that the cited references disclose no such direct relationship. That inflammatory bowel disease, for example, is related to the other diseases listed in the cited references (because they are all inflammatory diseases), is irrelevant to prove that the cited references disclose a direct relationship between CD81, inflammatory bowel disease, and an antibody. Because the rejection is sustained on a proposition not supported by law, the rejection must be withdrawn.

Second, Applicants respectfully disagree with the Office’s conclusion that the relied-upon portions of Curd *et al.* and Fleming *et al.* do not constitute *generic* disclosures. Analogous

to a generic chemical formula that recites several variable positions at which a myriad of substituents are listed as being suitable, *see Arkley, Fleming et al.* (and to a greater extent Curd *et al.*) *generically* discloses treatment of a disease with an agent, and provides a laundry list of both agents and diseases that can be selected in such a generic method. In the case of Curd *et al.*, this is further compounded by the fact that CD81 must also be selected from a laundry list of different B-cell markers.

However, as Applicants have already noted on the record,<sup>1</sup> the *combination* of CD81, antibody, and inflammatory bowel disease claimed by Applicants is a species that must be selected from the generic disclosures of Curd *et al.* and Fleming *et al.* Because this *species* is not disclosed either expressly or inherently by either reference, to hold that it is described for purposes of anticipation requires the creation, *ex post facto*, of this species by picking and choosing from the laundry lists of Curd *et al.* and Fleming *et al.* - which when taken together constitute a **genus** of possible treatment methods. Applicants maintain that the generic disclosures of Curd *et al.* and Fleming *et al.* are sufficiently broad, and the species of methods encompassed therein sufficiently diverse, that they do not disclose the claimed combination with “sufficient specificity,” as is required for a genus to anticipate a species. *See In re Ruschig*, 343 F.2d 965, 974-75 (C.C.P.A. 1965).

In maintaining the rejection, the Office asserts that because CD81, inflammatory bowel disease, and an antibody are each *explicitly* named in Fleming *et al.* and Curd *et al.*, despite being located in different laundry lists of alternatives, anticipation is proper because when “the [claimed] species is clearly named, the species claim is anticipated no matter how many other

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<sup>1</sup> *See, e.g.*, pages 7-10 of the Amendment filed October 6, 2010.

species are additionally named,” citing M.P.E.P. § 2131.02 and *Ex parte A*. However, Applicants respectfully submit that this assertion is also predicated on a misunderstanding of the law. As acknowledged by the Office, M.P.E.P. § 2131.02 and *Ex parte A* pertain to the situation where the *species* itself is explicitly named. As noted above, the relevant species in the instant case is the combination of CD81, antibody, and inflammatory bowel disease - and this *specific combination* is not explicitly named, or inherently disclosed, anywhere in Fleming *et al.* and Curd *et al.* To the contrary, it can only be obtained by picking and choosing from the laundry list disclosures therein. This clearly is not a species that is “clearly named,” under M.P.E.P. § 2131.02 and *Ex parte A*; such would require an express and specific disclosure of using an anti-CD81 antibody to treat inflammatory bowel disease, without any selection from any alternatives being required. Clearly this is not the case with either Fleming *et al.* and Curd *et al.*

In view of the foregoing, Applicants respectfully submit that the bases on which the anticipation rejections are sustained are unsupported by law, and accordingly, the rejections should be withdrawn.

In addition to Fleming *et al.* and Curd *et al.* failing to *describe* the presently claimed invention with sufficient specificity for purposes of anticipation, as a corollary, neither reference enables the presently claimed method. As Applicants have previously pointed out, prior art containing broad disclosures of alternatives is non-enabling, and thus not anticipatory, where undue experimentation would be required to determine which combinations of alternatives are operable. *See, e.g., Impax Laboratories, Inc. v. Aventis Pharmaceuticals, Inc.*, 545 F.3d 1312 (Fed. Cir. 2008). In *Impax*, the district court acknowledged that the allegedly anticipating disclosure contemplated that the compounds of the invention “are associated with the treatment

of at least 8 different diseases.”<sup>2</sup> However, the court held that there “was nothing in the [disclosure] which would lead one to recognize that any specific compound, let alone riluzole, would be used to treat any specific disease.”<sup>3</sup> The court concluded that it would require undue experimentation to determine what compounds of the invention can be sued to treat each disease listed. The Federal Circuit affirmed the district court’s reasoning, stating that it would have required “extensive experimentation to link riluzole with the treatment of ALS [the subject matter of the claim at issue].”

Similarly, in the instant case, Applicants respectfully submit that those of ordinary skill in the art would not have recognized that any of the compositions of Fleming *et al.* and Curd *et al.* could be used to treat any of the diseases recited therein; the mere listing of a plethora of alternative treatments, and a plethora of alternative diseases to be treated, is not in itself sufficient to place the public in possession of the presently claimed invention.

For this reason also, Applicants maintain that the presently claimed invention is not anticipated.

Withdrawal of these rejections is respectfully requested.

**Claims 31, 33, 34 and 35 Are Patentable Under 35 U.S.C. § 103(a)**

1. On page 8 of the Office Action, Claims 31, 33 and 34 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,423,501, WO 98/25647 or

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<sup>2</sup> See *Impax Laboratories, Inc. v. Aventis Pharmaceuticals, Inc.*, 496 F.Supp.2d 428, 432-33 (D. Del. 2007).

<sup>3</sup> *Id.*

WO 00/67796, in view of Owens *et al.*, for the reasons set forth in the Office Action mailed April 7, 2010.

2. On page 10 of the Office Action, Claim 31 is rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,423,501 or WO 98/25647 in view of Owens *et al.*, for the reasons set forth in the Office Action mailed April 7, 2010.

In making these rejections, the Examiner relies upon Fleming *et al.* and Curd *et al.* for the same reasons as in the anticipation rejections discussed above. However, the Examiner acknowledges that neither Fleming *et al.* nor Curd *et al.* discloses or suggests using a Fab, F(ab')<sub>2</sub>, Fv or scFv. In an attempt to rectify such deficiency, the Examiner cites to Owens *et al.*, who allegedly discloses the production of single chain antibodies, Fab fragments, and F(ab')<sub>2</sub> fragments.

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

Initially, Applicants note that Owens *et al.* is directed to the production of variant antibody molecules, such as Fab, F(ab')<sub>2</sub>, Fv or scFv molecules. As such, Owens *et al.* does nothing to rectify the deficiencies of Fleming *et al.* and Curd *et al.*, discussed above. Accordingly, those of ordinary skill in the art would not have arrived at the presently claimed invention for the same reasons as presented above, notwithstanding the disclosure of Owens *et al.*

Withdrawal of these rejections is respectfully requested.

**Claims 19, 20 and 31-37 are Patentable Under 35 U.S.C. § 103(a)**

1. On page 9 of the Office Action, Claims 19, 20 and 31-37 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over US. Patent No. 6,423,501 or WO 98/25647 for the reasons set forth in the Office Action mailed April 7, 2010.

2. On page 9 of the Office Action, Claims 19, 20 and 31-37 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over WO 00/67796 for the reasons set forth in the Office Action mailed April 7, 2010.

The Examiner appears to have found Applicants' previous arguments unpersuasive, asserting that those of ordinary skill in the art would readily have used anti-CD81 antibodies to treat inflammatory bowel disease, and would have possessed at least a reasonable expectation of success in doing so.

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

To sustain a finding of obviousness, those of ordinary skill in the art at the time of the invention must have possessed a reasonable expectation of success in carrying out the claimed invention.<sup>4</sup> This "reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure."<sup>5</sup>

Applicants respectfully submit that, even assuming *arguendo* that Fleming *et al.* or Curd *et al.* suggests, amongst a plethora of other treatment methods, the possibility of treating inflammatory bowel disease by administering an anti-CD81 antibody, those of ordinary skill in

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<sup>4</sup> See *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

<sup>5</sup> *Id.*



the art *at the time of the invention* would not have possessed a reasonable expectation of success in treating inflammatory bowel disease with an anti-CD81 antibody.

This is, in part, because they would have recognized not only a predominant role for pro-inflammatory cytokines, such as TNF- $\alpha$ , in the pathogenesis of inflammatory bowel disease, but they would also have recognized the pivotal role of T-lymphocyte activation in the production of such pro-inflammatory cytokines in the bowel mucosa.

Specifically, Neurath *et al.* (*Eur. J. Immunol*, 1997, 27:1743-1750),<sup>6</sup> authored by Markus Neurath, an internationally-recognized authority on inflammatory bowel disease research, discloses that TNF- $\alpha$  has a predominant pathogenic role in colitis in mice.<sup>7</sup> For example, Neurath *et al.* experimentally demonstrates that macrophages in the lamina propria produced high levels of TNF- $\alpha$  in inflammatory bowel disease, and notes that the majority of recent colitis models have revealed that the inflammation is mediated by CD4<sup>+</sup> T-lymphocytes producing high amounts of IFN- $\gamma$  and TNF- $\alpha$ .<sup>8</sup>

Further, Montfrans *et al.* (*Mediators of Inflammation*, 1998, 7:149-152)<sup>9</sup> discloses that, following analysis of numerous studies on a variety of different inflammatory bowel disease animal models, the collective conclusion is that an overactive “antigen-dependent( CD4<sup>+</sup>) T lymphocyte activation will result in a high production of pro-inflammatory cytokines within the

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<sup>6</sup> In accordance with M.P.E.P. 609.05(c), the document cited herein in support of Applicants’ remarks is being submitted as evidence directed to an issue raised in the Office Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08 or PTO-1449 is believed to be necessary.

<sup>7</sup> See the paragraph bridging pages 1743-1744 of Neurath *et al.*

<sup>8</sup> See page 1749, column 1, 2<sup>nd</sup> paragraph, of Neurath *et al.*

<sup>9</sup> In accordance with M.P.E.P. 609.05(c), the document cited herein in support of Applicants’ remarks is being submitted as evidence directed to an issue raised in the Office Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08 or PTO-1449 is believed to be necessary.

mucosal compartment and [result] in inflammatory bowel disease.”<sup>10</sup> Accordingly, Montfrans *et al.* and Neurath *et al.*, published prior to the time of the invention (and which form part of the state of the art at the time of the invention), demonstrate the predominant role for an overactive proinflammatory T-cell response, and the resulting overproduction of TNF- $\alpha$  by T-lymphocytes and macrophages, in inflammatory bowel disease. These animal studies confirmed previous observations in humans, in which hyperresponsive T-lymphocytes localizing to the lamina propria in patients with inflammatory bowel disease were posited to contribute to local inflammation.<sup>11</sup>

In contrast, however, Fleming *et al.* posits that inhibition of CD81 may inhibit mast cell degranulation, and lists inflammatory bowel disease, in amongst a plethora of other diseases, as a disease that may potentially be treated by inhibiting CD81 (to inhibit mast cell degranulation). However, as shown by the above evidence - reflective of the knowledge of those of ordinary skill in the art at the time of the invention - it was understood that TNF- $\alpha$  production by *T-lymphocytes and macrophages* mediated the predominant inflammatory response in inflammatory bowel disease. For this reason, those of ordinary skill in the art would not have possessed a reasonable expectation of success in treating inflammatory bowel disease by targeting CD81 on mast cells - because they would have appreciated that such a method would not have targeted the predominant inflammatory response.

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<sup>10</sup> See page 150, column 1, 1<sup>st</sup> paragraph, of Montfrans *et al.*

<sup>11</sup> See page 571, column 1, 2<sup>nd</sup> paragraph, of Emmrich *et al.* (*Lancet*, 1991, 338:570-571); in accordance with M.P.E.P. 609.05(c), the document cited herein in support of Applicants' remarks is being submitted as evidence directed to an issue raised in the Office Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08 or PTO-1449 is believed to be necessary.

Similarly, Curd *et al.* posits that inhibition of CD81 on *B-cells* may be used for the treatment of autoimmune diseases. Curd *et al.* lists inflammatory bowel disease, in amongst a plethora of other diseases, as an autoimmune disease that may potentially be treated by inhibiting CD81. For the same reasons, however, those of ordinary skill in the art would not have possessed a reasonable expectation of success in treating inflammatory bowel disease by targeting CD81 on B-cells - because they would have appreciated that such a method would not have targeted the predominant inflammatory response.

In addition to the above, Applicants respectfully point out that those of ordinary skill in the art would not have possessed a reasonable expectation of success in treating inflammatory bowel disease by administering an anti-CD81 antibody because of the broad expression, and differential effects, of CD81 on other cell types. As stated by Witherden *et al.* (*J. Immunol.*, 2000, 165:1902-1909),<sup>12</sup> “CD81 ... is expressed on a wide variety of tissues and cell types, including both B and T cells as well as epithelial cells, and has the capacity to associate with other cell surface proteins in a cell type-specific manner.”<sup>13</sup> Thus, at the time of the invention, CD81 was known to be expressed on a wide variety of different cell types, and to interact with a variety of different cell surface proteins “in a cell type-specific manner.”<sup>14</sup>

In particular, Witherden *et al.* specifically discloses that CD81 was known at the time of the invention to be expressed, *inter alia*, on B-cells and T-cells. However, Witherden *et al.*

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<sup>12</sup> In accordance with M.P.E.P. 609.05(c), the document cited herein in support of Applicants’ remarks is being submitted as evidence directed to an issue raised in the Office Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08 or PTO-1449 is believed to be necessary.

<sup>13</sup> See page 1902, 2<sup>nd</sup> column, 2<sup>nd</sup> paragraph, of Witherden *et al.*

<sup>14</sup> See page 1902, 2<sup>nd</sup> column, 2<sup>nd</sup> paragraph, of Witherden *et al.*

demonstrates that when CD81 on T-cells is targeted with antibody, it stimulates T-cell activation,<sup>15</sup> resulting in enhanced production of proinflammatory cytokines, such as TNF- $\alpha$  and IFN- $\gamma$ .<sup>16</sup> Therefore, because those of ordinary skill in the art at the time of the invention appreciated the predominant role of an overactive proinflammatory T-cell response - and the resulting TNF- $\alpha$  production by T-lymphocytes and macrophages - in *causing* inflammatory bowel disease (discussed above), they would not have possessed a reasonable expectation of success in treating inflammatory bowel disease by administering an anti-CD81 antibody. This is because they would have recognized that, even when targeting CD81 on B-cells and mast cells, as posited by Curd *et al.* and Fleming *et al.*, respectively, T-cells would also be targeted - resulting in enhanced production of proinflammatory cytokines such as TNF- $\alpha$ . Accordingly, due to the broad expression of CD81 on different cell types, and the cell type-specific functions of CD81 - in particular the stimulation of T-cells when cell-surface CD81 on T-cells is targeted by antibody - those of ordinary skill in the art would not have possessed any expectation that administering an anti-CD81 antibody would be effective in treating inflammatory bowel disease, much less possessed a reasonable expectation of success, as obviousness requires.

Applicants note that it is well-settled that in any obviousness inquiry, the person of ordinary skill in the art is a hypothetical person who is presumed to have known the *relevant art at the time of the invention*.<sup>17</sup> Certainly, at the time of the invention, Neurath *et al.* (and

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<sup>15</sup> See Figure 1 of Witherden *et al.*

<sup>16</sup> See Figure 6B of Witherden *et al.*

<sup>17</sup> See *In re GPAC*, 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995); *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 962, 1 USPQ2d 1196, 1201 (Fed. Cir. 1986) and; *Environmental Designs, Ltd. V. Union Oil Co.*, 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983).

Montfrans *et al.*, Emmrich *et al.* and Witherden *et al.*) would have been highly relevant to those of ordinary skill in the pertinent art contemplating targeting CD81 to treat inflammatory bowel disease. As such, the disclosures of Neurath *et al.*, Montfrans *et al.*, Emmrich *et al.* and Witherden *et al.* are highly relevant to this obviousness inquiry.

In sum, Applicants respectfully submit that a reasonable expectation of success could not have existed prior to an experimental demonstration of efficacy, due to the unpredictability of the net effect of targeting CD81 - particularly when the state of the art at the time of the invention recognized that targeting CD81 can enhance proinflammatory cytokine production (such as TNF- $\alpha$ ). Applicants have shown, however, through *in vivo* experimentation in the specification as filed, that targeting CD81 is effective in treating inflammatory bowel disease, which could not have been predicted or expected from the state of the art at the time of the invention. As noted above, the “reasonable expectation of success must be founded in the prior art, not in the applicant’s disclosure.”<sup>18</sup> (Emphasis added.)

In view of the foregoing, Applicants respectfully submit that those of ordinary skill in the art at the time of the invention would not have possessed a reasonable expectation of success in treating inflammatory bowel disease by administering an anti-CD81 antibody, precluding a finding of obviousness.<sup>19</sup>

Withdrawal of these rejections is respectfully requested.

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<sup>18</sup> *Vaeck*, 947 F.2d at 493.

<sup>19</sup> *Id.*

### **Conclusion**

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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